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(54) ORAL SOLID PREPARATION

(57) The invention is to provide an oral solid pharmaceutical that is uniform in the content of KRP-197, having bladder-selective anticholinergic activity, being a therapeutic drug for pollakiuria and urinary incontinence, and being active with a very low dosage, that can be taken quantitatively, and that is easy in the handling. Since KRP-197 becomes unstable to light under the influence of additives, the invention is to select the additives to be used and to obtain a pharmaceutical with high stability.

By formulating KRP-197 with drug-making carriers, a pharmaceutical that is uniform in the content, capable of taking quantitatively and easy in the handling has been provided. Furthermore, by using polyvinyl pyrrolidone for binder and by making into tablet coated with a coating base containing titanium dioxide and ferric oxide, a pharmaceutical capable of taking quantitatively and excellent in the light stability has been provided.

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Description

Technical field

[0001] The present invention relates to an oral solid pharmaceutical with a small amount of powder of 4-(2-methyl-1-imidazolyl)-2,2-diphenylbutylamide (hereinafter abbreviated as KRP-197), having selective anticholinergic activity on bladder and being a therapeutic drug for pollakiuria and urinary incontinence, made into an oral tablet capable of taking easily.

Background technologies

[0002] KRP-197 is a novel derivative having selective anticholinergic activity (Japanese Unexamined Patent Publication No. Hei 7-15943) and is promising as a therapeutic drug for pollakiuria and urinary incontinence (Miyachi H. et al, Bioorg. Med. Chem., 1999, 7, 1151-1161). No oral solid pharmaceutical that is uniform in the content of a small amount of active ingredient, excellent in the stability and capable of taking quantitatively on clinical application of KRP-197 has been known.

[0003] The subject of the invention is to provide an oral solid pharmaceutical that is uniform in the content of active ingredient contained in a small amount and capable of taking quantitatively. Additionally, since KRP-197 becomes unstable to light under the influence of additives, the subject is to provide an oral solid pharmaceutical with excellent stability to light.

Disclosure of the invention

[0004] The inventors have prepared an oral solid pharmaceutical that contains a small amount of active ingredient uniformly and is capable of taking quantitatively on clinical application of KRP-197, leading to the completion of the invention. The inventive oral solid pharmaceutical is an oral solid pharmaceutical (tablet) with uniform content, prepared by formulating a small amount of KRP-197 with drug-making carriers (excipient, disintegrator, binder, lubricant and coating agent) and by granulating, pressing into tablet and coating.

[0005] According to the invention, by formulating a small amount of powder of KRP-197 with drug-making carriers and making into tablet, a pharmaceutical easy to take quantitatively can be provided. Moreover, by using polyvinyl pyrrolidone as a binder and further by coating with a coating solution containing titanium dioxide and ferric oxide, a pharmaceutical with uniform content and good light stability can be provided.

[0006] The process for preparing the inventive pharmaceutical comprises the steps of mixing the excipient (for example, saccharides such as lactose and glucose, sugar alcohols such as D-sorbitol and mannitol, celluloses such as microcrystalline cellulose, starches such as partially pregelatinized starch and corn starch, etc., preferably partially pregelatinized starch, lactose or microcrystalline cellulose) and the disintegrator (for example, celluloses such as calcium carboxymethylcellulose, low substituted hydroxypropylcellulose, sodium cross carmelose and methylcellulose, cross povidone, etc., preferably low substituted hydroxypropylcellulose), and further by adding the binder (for example, celluloses such as hydroxypropylcellulose, hydroxypropylmethylcellulose, ethylcellulose and methylcellulose, gelatin, polyvinyl alcohol, partially hydrolyzed polyvinyl alcohol, polyvinyl pyrrolidone, etc., preferably partially hydrolyzed polyvinyl alcohol or polyvinyl pyrrolidone), followed by granulation. The granulation can be performed by wet granulation process, fluidized bed granulation process or dry granulation process, but, at this time, the fluidized bed granulation process can be used well.

[0007] Following this, the lubricant (for example, magnesium stearate, calcium stearate, talc, hydrogenated oil, etc., preferably magnesium stearate) is added, the mixture is pressed into tablet, and further the coating agent (for example, celluloses such as hydroxypropylcellulose, hydroxypropylmethylcellulose, ethylcellulose and methylcellulose, hydroxypropylmethylcellulose phthalate, methacrylic acid copolymer, titanium dioxide, ferric oxide, carnauba wax, etc., preferably hydroxypropylmethylcellulose, titanium dioxide, ferric oxide or carnauba wax) is coated, thereby the oral solid pharmaceutical or tablet capable of taking more easily can be obtained.

[0008] Furthermore, the preparation of oral solid pharmaceutical with improved light stability can be accomplished by using polyvinyl pyrrolidone as a binder and further by coating with a coating solution containing titanium dioxide and ferric oxide. Upon granulation at this time, an aqueous solution containing KRP-197 and polyvinyl pyrrolidone is sprayed and granulation and drying are performed, followed by addition of lubricant, pressing into tablet, and coating. At this time, if coating with a coating solution containing titanium dioxide and ferric oxide, a tablet with improved stability to light as well as uniform content can be obtained.

[0009] In the tablet obtained in this way, 0.025mg to 2mg of KRP-197 can be contained uniformly as an active ingredient per tablet, and, by taking orally, the pharmaceutical can be taken quantitatively.

Best embodiment to put the invention into practice

[0010] In following, the invention will be illustrated based on the examples, but the invention is not confined to these examples.

(Example 1)

[0011] Per tablet, 0.05mg of KRP-197 and 16mg of partially pregelatinized starch were mixed, then 63.71mg of microcrystalline cellulose were added thereto and mixed. Further, 0.24mg of magnesium stearate were added and mixed, followed by pressing into tablet to obtain a plane tablet. Onto the plane tablet thus obtained, 4mg-equivalent hydroxypropylmethylcellulose 2910 was coated, and then 0.002mg of carnauba wax were added and mixed to obtain a film-coated tablet.

(Example 2)

[0012] Per tablet, 0.25mg of KRP-197 and 23mg of partially pregelatinized starch were mixed, then 92.45mg of microcrystalline cellulose were added thereto and mixed. Further, 0.3mg of magnesium stearate were added and mixed, followed by pressing into tablet to obtain a plane tablet. Onto the plane tablet thus obtained, 4mg-equivalent hydroxypropylmethylcellulose 2910 was coated, and then 0.002mg of carnauba wax were added and mixed to obtain a film-coated tablet.

(Example 3)

[0013] Per tablet, 2mg of KRP-197 and 24.6mg of partially pregelatinized starch were mixed, then 108mg of microcrystalline cellulose were added thereto and mixed. Further, 0.4mg of magnesium stearate were added and mixed, followed by pressing into tablet to obtain a plane tablet. Onto the plane tablet thus obtained, 5mg-equivalent hydroxypropylmethylcellulose 2910 was coated, and then 0.002mg of carnauba wax were added and mixed to obtain a film-coated tablet.

(Example 4)

[0014] Per tablet, 2mg of KRP-197, 86.85mg of lactose, 29mg of microcrystalline cellulose and 13.5mg of low substituted hydroxypropylcellulose were mixed, then an aqueous solution of 2.7 mg-equivalent partially hydrolyzed polyvinyl alcohol was added, and the mixture was milled, granulated and dried. Thereto, 5mg of magnesium stearate were added and mixed, followed by pressing into tablet to obtain a plane tablet. Onto the plane tablet thus obtained, 5mg-equivalent hydroxypropylmethylcellulose 2910 was coated, and then 0.002mg of carnauba wax were added and mixed to obtain a film-coated tablet.

(Example 5)

[0015] Per tablet, 0.025mg of KRP-197, 15.945mg of partially pregelatinized starch were mixed, then 63.79mg of microcrystalline cellulose were added thereto and mixed. Further, 0.24mg of magnesium stearate were added and mixed, followed by pressing into tablet to obtain a plane tablet. Onto the plane tablet thus obtained, 4mg-equivalent hydroxypropylmethylcellulose 2910 was coated, and then 0.002mg of carnauba wax were added and mixed to obtain a film-coated tablet.

(Example 6)

[0016] Per tablet, 18.7mg of partially pregelatinized starch and 74.975 mg of microcrystalline cellulose were taken. Then, using a fluidized bed granulation device, an ethanol-water solution of 0.025mg of KRP-197 and 1mg-equivalent polyvinyl pyrrolidone was sprayed thereto, and the mixture was granulated and dried. After screening and rectifying the granules, 0.3mg of magnesium stearate were added and mixed, followed by pressing into tablet to obtain a plane tablet. Onto the plane tablet thus obtained, a suspension of 4.5mg-equivalent hydroxypropylmethylcellulose 2910, 0.43mg-equivalent titanium dioxide and 0.07mg-equivalent ferric oxide was coated, and then 0.002mg of carnauba wax were added and mixed to obtain a film-coated tablet.

(Example 7)

[0017] Per tablet, 26.4mg of partially pregelatinized starch and 105.75 mg of microcrystalline cellulose were taken. Then, using a fluidized bed granulation device, an ethanol-water solution0.05mg of KRP-197 and 1.4mg-equivalent polyvinyl pyrrolidone was sprayed thereto, and the mixture was granulated and dried. After screening and rectifying the granules, 0.4mg of magnesium stearate were added and mixed, followed by pressing into tablet to obtain a plane tablet. Onto the plane tablet thus obtained, a suspension of 5.4mg-equivalent hydroxypropylmethylcellulose 2910, 0.52mg-equivalent titanium dioxide and 0.08mg-equivalent ferric oxide was coated, and then 0.002mg of carnauba wax were added and mixed to obtain a film-coated tablet.

(Example 8)

[0018] Per tablet, 26.4mg of partially pregelatinized starch and 105.7mg of microcrystalline cellulose were taken. Then, using a fluidized bed granulation device, an ethanol-water solution of 0.1mg of KRP-197 and 1.4mg-equivalent polyvinyl pyrrolidone was sprayed thereto, and the mixture was granulated and dried. After screening and rectifying the granules, 0.4mg of magnesium stearate were added and mixed, followed by pressing into tablet to obtain a plane tablet. Onto the plane tablet thus obtained, a suspension of 5.4mg-equivalent hydroxypropyl-methylcellulose 2910, 0.52mg-equivalent titanium dioxide and 0.08mg-equivalent ferric oxide was coated, and then 0.002mg of carnauba wax were added and mixed to obtain a film-coated tablet.

(Example 9)

[0019] Per tablet, 30.4mg of partially pregelatinized starch and 121.35 mg of microcrystalline cellulose were taken. Then, using a fluidized bed granulation device, an ethanol-water solution of 0.25mg of KRP-197 and 1.6mg-equivalent polyvinyl pyrrolidone was sprayed thereto, and the mixture was granulated and dried. After screening and rectifying the granules, 0.4mg of magnesium stearate were added and mixed, followed by pressing into tablet to obtain a plane tablet. Onto the plane tablets thus obtained, a suspension of 5.4mg-equivalent hydroxypropyl-methylcellulose 2910, 0.52mg-equivalent titanium dioxide and 0.08mg-equivalent ferric oxide was coated, and then 0.002mg of carnauba wax were added and mixed to obtain a film-coated tablet.

(Experimental example 1)

[0020] With the tablets containing 0.025mg of KRP-197 obtained in Example 5 and Example 6, which are most liable to be influenced by additives in the stability, decomposition products under light irradiation of up to 1.2 million Lux·hr in the non-packaged state were determined by high-speed liquid chromatograph method. As a result, the tablet obtained in Example 6 showed good stability, hence the effect of additions of polyvinyl pyrrolidone, titanium dioxide and ferric oxide was ascertained. The measurement results of decomposition products are shown in Table 1.

Table 1.

Evaluation results of stability of 0.025mg KRP-197 tablet (content of main decomposition products, %)		
	Example 5	Example 6
Start	No detection	No detection
1.2 million Lux·hr	13.6%	<0.16%

(Experimental example 2)

[0021] With the tablets obtained in respective examples from Example 1 through Example 9, results obtained according to the uniformity test of content in the 13th revision Japanese Pharmacopoeia are shown in Table 2.

Table 2.

Test results of uniformity of content of KRP-197 tablet									
	Example 1	Example 2	Example 3	Example 4	Example 5	Example 6	Example 7	Example 8	Example 9
Av. value (5)	96.1	96.2	100.6	98.8	99.0	99.5	100.4	100.3	101.1
Range (%)	93.0~98.2	94.6~97.6	97.5~100.1	97.5~100.1	97.0~100.6	97.2~102.7	99.0~101.3	99.7~101.4	99.7~102.4
Judgment value (%)	7.9	6.0	3.7	3.2	4.1	2.6	1.9	1.5	2.8
Judgment value: Value less than 15% conform to the standard.									

Utilizability in the industry

[0022] According to the invention, by formulating KPP-197, having bladder-selective anticholinergic actibity and being a therapeutic drug for pollakiuria and urinary incontinence, with drug-making carriers and by converting to tablet, it has become possible to make the active ingredient that was difficult to take quantitatively, if keeping it powdery as it is, because of extremely small amount, into an oral solid pharmaceutical that is uniform in the content of ingredient and also easy in the handling, thus allowing to take quantitatively. In addition, by using polyvinyl pyrrolidone for binder and using titanium dioxide and ferric oxide for coating base, it has become possible to provide a pharmaceutical with improved stability to light.

Claims

1. An oral solid pharmaceutical comprising 4-(2-methyl-1-imidazolyl)-2,2-diphenylbutylamide as an active ingredient and drug-making carriers.

2. The oral solid pharmaceutical of Claim 1, wherein the drug-making carriers comprise excipient, lubricant and coating agent, or, in addition to these, they include further disintegrator and/or binder.

3. The oral solid pharmaceutical of Claim 2, wherein the excipient comprises partially pregelatinized starch, lactose and microcrystalline cellulose, the disintegrator comprises low substituted hydroxypropylcellulose, the binder comprises partially hydrolyzed polyvinyl alcohol and polyvinyl pyrrolidone, the lubricant comprises magnesium stearate, and the coating agent comprises hydroxypropylmethylcellulose, titanium dioxide, ferric oxide and carnauba wax.

4. The oral solid pharmaceutical with excellent light stability of Claim 2, wherein the binder is polyvinyl pyrrolidone, and the essential components of coating agent are titanium dioxide and ferric oxide.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP00/07904

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] A61K31/4164, 9/20, 9/36, 47/36, 47/26, 47/38, 47/32, 47/02, A61P13/02, C07D233/60

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] A61K31/4164, 9/20, 9/36, 47/36, 47/26, 47/38, 47/32, 47/02, A61P13/02, C07D233/60

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Jitsuyo Shinan Koho	1926-1992	Toroku Jitsuyo Shinan Koho	1994-1996
Kokai Jitsuyo Shinan Koho	1971-1992	Jitsuyo Shinan Toroku Koho	1996-2000

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP, 733621, A1 (KYORIN PHARMACEUTICAL CO.,LTD.), 25 September, 1996 (25.09.96),	1
Y	PAGE 8 LINE 15,Example 11,Experimental example & JP, 7-215943, A	2-4
Y	JP, 11-255649, A (Dainippon Ink and Chemicals, Inc.), 21 September, 1999 (21.09.99), Par. Nos. [0035] to [0051] (Family: none)	2-4
Y	EP, 901787, A1 (Takeda Chemical Industries, Ltd.), 17 March, 1999 (17.03.99), Full text & JP, 11-147819, A	4
Y	JP, 58-206533, A (Teijin Limited), 01 December, 1983 (01.12.83), Full text (Family: none)	4
Y	EP, 314387, A1 (ELI LILLY AND COMPANY), 03 May, 1989 (03.05.89), Full text	4

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
16 January, 2001 (16.01.01)	30 January, 2001 (30.01.01)
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Facsimile No.	Telephone No.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP00/07904

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	& JP, 1-146821, A	

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